III. "Contributions to the Study of the Connexion between Chemical Constitution and Physiological Action. Part II." By T. Lauder Brunton, M.D., F.R.S., and J. Theodore Cash, M.D., F.R.S. Received March 2, 1891.

(Abstract.)

In a former paper, the authors discussed the alterations which are produced in the action of ammonia by the substitution of alkyl radicals for hydrogen, and by combination of the compound ammonias with different acid radicals.

In the present paper, they have examined on a similar plan the physiological action of some bodies of the aromatic series.

The research was begun more than four years ago, a preliminary communication having been made to this Society on March 24th, 1887. A good deal of work has been done in connexion with the subject by other observers while the research was in progress. The results obtained by others, however, are not easy of comparison, while the experiments of the authors, having been made as nearly as possible under the same conditions, yield results which are more easily compared, so as to allow of general conclusions being drawn from them. They have examined (1) the physiological action of benzene, and (2) the alterations which occur in its action when one or more atoms of hydrogen in it are replaced by (*a*) haloid radicals, (*b*) alcohol radicals, (*c*) by hydroxyl, (*d*) by NO_2, and (*e*) by amidogen, NH_2.

They have also examined the modifications in the action of various members of the series by changes in temperature.

They describe the general symptoms produced by benzene and its compounds in frogs and rats, their action on muscle and nerve, on reflex action, on respiration, and circulation.

They describe a new method of registering the blood pressure and pulse, using a slow drum for the former, and a quick one for the latter, so as to have the whole course of the blood pressure during an experiment given in a comparatively short tracing, while samples of the pulse waves are taken at various periods.

They find that the action of benzene and its compounds is chiefly exerted on the spinal cord, although they act also on the cerebrum and, to a slight extent, on nerves and muscle. Their effect on muscle and nerve is to weaken them, the paralysing action being stronger upon the nerve than the muscle.

Their action on the cerebrum is evidenced by lethargy and disinclination to voluntary movement both in frogs and rats.

Their action on the spinal cord appears to consist in producing

increased excitability, greater diffusion of stimuli with diminished power and definiteness of movement. Thus slight stimuli in the frog produce movement more readily in the poisoned than in the normal condition, but the movement, instead of being limited to one limb, vigorous and steady, is diffused over several limbs, feeble and tremulous or jerking.

In frogs, the tremors or jerking always occur on attempted movement, and sometimes, to a slight extent, when at rest. If the dose be large, they are succeeded by paralysis. Absorption of the drug is slow and irregular, and it may cause local rigor of the muscles. The heart remains long irritable.

Haloid radicals do not modify the action of benzene to the same extent as they do that of ammonia, but they do so in somewhat the same direction as the authors described in their former paper on this subject. Monochlorobenzene affects the spinal cord more than benzene, causing spasm and rapid diminution of reflex. It also weakens the circulation, but does not seem to affect motor nerves or muscles more than benzene. The bromo- and iodo-compounds have a more powerful paralysing action on the cerebrum than benzene and chlorobenzene, and the compound of iodine with benzene, like its compound with ammonia, appears to have a special tendency to paralyse motor nerves, muscles, and cerebral reflexes, and to depress the heart. Heat accelerated and cold retarded the action of the substances.

The substitution of alcohol radicals for hydrogen in benzene appears to modify its action in much the same way as one would expect from a general consideration of the properties of the alcohol group, which, as a rule, have a sedative action on the nervous system.

The compounds of benzene with alcohol radicals produce less tremor, less hyperæsthesia, and greater lethargy than the halogen compounds. The circulation is little affected by them. They have little action on muscle or nerve, but act more powerfully on the nerve than on the muscle. Their action appears to be more fleeting than that of the halogen compounds. Trimethylbenzene (mesitylene) was more active than methyl- or dimethyl-benzene. In poisoning by dimethylbenzene a curious increase of reflex action was observed, after it had almost gone, and spontaneous movement had quite gone.

Substitution of hydrogen by hydroxyl increases the tendency to convulsions. These are due to the action of the substances on the spinal cord and not on the cerebrum; they occur independently of voluntary movement, except when the dose is very small, and continue almost unchanged after destruction of the cerebrum. Slight tremor may occur before destruction of the cerebrum, but it is greatly masked by the powerful contractions referred to. The position of the

hydroxyl groups in the di- and tri-oxybenzenes affects their physiological action. Para-oxybenzene (resorcin) has an action similar in kind, but weaker than the ortho- and meta-oxybenzenes (hydroquinone and pyrocatechin). The most characteristic feature of its action is the occurrence, at nearly regular intervals, of clonic convulsions, which never become tonic or tetanic, and are due to the action of the drug on the cord. They are abolished by the action of curare, even in a limb protected by ligature from the action of both poisons. Strychnine produces tetanic spasm in a frog poisoned by resorcin, if the symptoms due to the latter drug are only imperfectly developed, but does not do so if the clonic spasms have become well marked. Large doses cause paralysis, destroying the irritability and conducting power of the cord. Trioxybenzene (1 : 2 : 3-pyrogallol) produces more lethargy than resorcin, less tremor on movement, and little spontaneous jerking. Its power to produce immediate symptoms in the frog is only one-fourth or one-fifth that of resorcin, but it is almost exactly equal to it in its ultimate lethal power.

Amidobenzene (anilin) may be regarded either as benzene with one hydrogen replaced by amidogen, NH_2, or as ammonia in which one hydrogen is replaced by phenyl, C_6H_5. In conformity with this constitution, the symptoms produced by it differ from those of benzene and resemble those of ammonia in the tendency to more violent spasm and to greater paralysis of muscle and nerve. They differ from those of ammonia in the fact that the convulsions never assume the form of true tetanus, the tetanic spasm which the ammonia group would produce being broken up, so to speak, by the action of the phenyl. With the exception of the hydroxyl compounds, amidobenzene causes the most rapid occurrence of motor phenomena. It produces great tremor after a spring and active incoordinate movement, but no tonic spasm. Nitrobenzene causes lethargy with increasing tremor on movement, and early abolition of reflex action.

The effect of several benzene compounds on reflex time was observed. The oxybenzenes could not be tested on account of the spontaneous jerks to which they give rise. The general action is to cause a lengthening in the reflex time, but a primary shortening was observed frequently in the case of chlorobenzene, slightly in methyl-, dimethyl-, and ethyl-benzene.

In producing muscular rigor, chlorobenzene is considerably more powerful than the bromo- or iodo-compound, and is intermediate in strength between methyl- and dimethyl-benzene. Of the methylbenzenes, the methyl- is the strongest, the dimethyl- next, and the trimethyl- weakest. The action of these compounds on muscles is, therefore, inversely to the amount of methyl substituted for hydrogen in the benzene molecule. Ethyl benzene is nearly the same strength as methyl, and stronger than the dimethyl or trimethyl com-

pounds. Amidobenzene and nitrobenzene are less active in producing rigor.

The respiration is considerably and early affected in warm-blooded animals (cats) by benzene and its compounds. There is usually a primary acceleration, followed by slowing. The heart appeared to stop before the respiration in poisoning by benzene and its haloid compounds, by ethylbenzene, amidobenzene, and nitrobenzene, whilst respiration usually failed before the heart, or nearly at the same time, in poisoning by the methylbenzenes and oxybenzenes.

The first effect of the benzene compounds on the pulse or on blood pressure is usually a quickening of the pulse and a rise in the pressure. This is followed by slowing of the pulse and fall of the pressure.

In their preliminary communication in 1887, the authors directed attention to the curious resemblance between the tremor caused by benzene and some other aromatic substances in frogs and the symptoms of disseminated sclerosis in man. In the present paper, they point out also the likeness between the violent slapping movements caused in the frog by some of the haloid compounds of benzene, as well as by amidobenzene, and the symptoms of locomotor ataxy in man.

IV. "The Physiological Action of the Paraffinic Nitrites considered in connexion with their Chemical Constitution. Part I. The Action of the Paraffinic Nitrites on Blood Pressure." By J. THEODORE CASH, M.D., F.R.S., Professor of Materia Medica in the University of Aberdeen, and WYNDHAM R. DUNSTAN, M.A., Professor of Chemistry to the Pharmaceutical Society of Great Britain. Received March 4, 1891.

(Abstract.)

CONTENTS.

The present investigation was commenced three years ago, in order to throw further light on the mode of action of the paraffinic nitrites when introduced into the animal organism, and particularly to deter-